

**Supplementary Figure Legends.**

**Supplementary Figure S1: Chemical Structures of top 12 molecules identified in the pathogen box screen as schizont inhibitors.** These structures are obtained from PubChem (<https://pubchem.ncbi.nlm.nih.gov>) and MolView (<http://molview.org/>)

**Supplementary Figure S2: Heat Map showing inhibition of parasite stage transition upon treatment with the most potent 90 molecules.** Stage-specific inhibitory potential for 90 most potent molecules ( $EC_{50} \leq 1 \mu M$ ) were analyzed by phenotype screening. The data shown are mean values of two biological replicates.

**Supplementary Figure S3: Effect of schizonticidal inhibitors on merozoite segmentation/maturation.** Immunofluorescence analysis on drug-treated parasites using an antibody against glideosome-associated protein (GAP45), a marker for mature merozoites indicating segmentation of merozoites; PlasmoDB GeneID: PF3D7\_1222700, Glideosome-associated protein (GAP45).

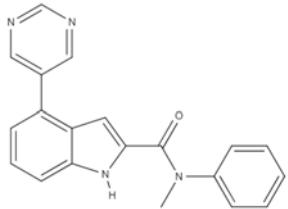
**Supplementary Figure S4: Evaluation of egress inhibitors towards blocking merozoite invasion of the RBC.** Molecules that affected schizont-ring transition, to some extent affected merozoite invasion at  $3 \mu M$  as indicated by phenotypes obtained from Giemsa-stained smears (A). However, merozoite inhibition was not affected at a lower inhibitor concentration of  $1 \mu M$ , as indicated by flow cytometry based estimation of merozoite invasion events in presence of the inhibitors (B).

**Supplementary Table 1: Molecules from other diseases exhibiting antimalarial activity.** List of 62 antimalarial compounds from Pathogen Box showing chemical class, consolidated study result and predicted cellular targets.

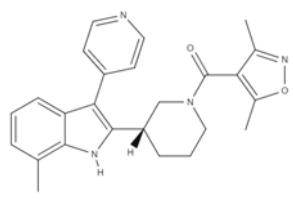
**Supplemental Dataset 1 (excel file): Consolidated dataset of phenotypic screens of the MMV pathogen Box against *P. falciparum* erythrocytic stages.**

# Fig S1

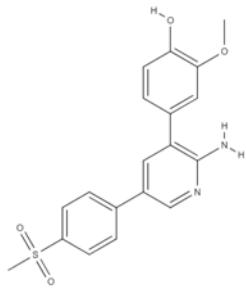
## Chemical Structure of 12 Schizont Inhibitors



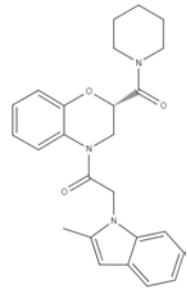
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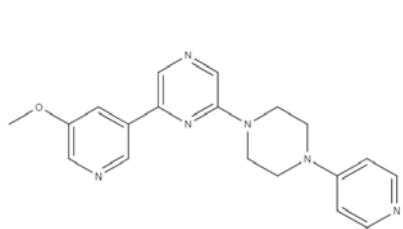
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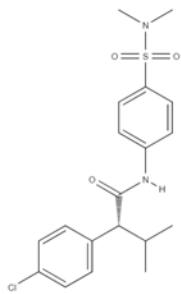
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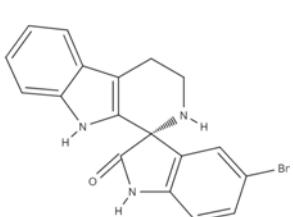
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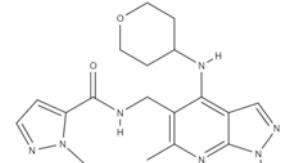
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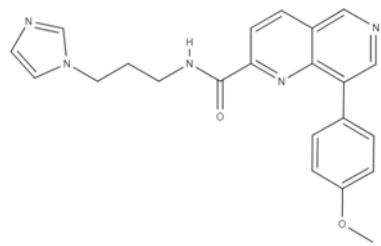
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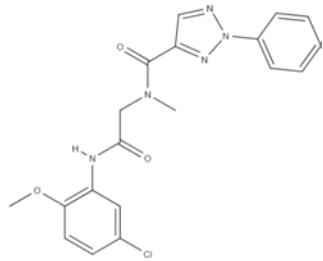
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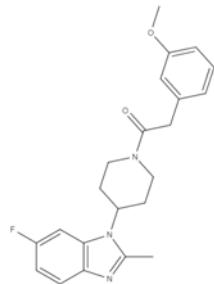
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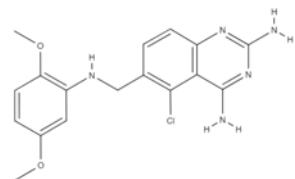
MMV020670



MMV020710

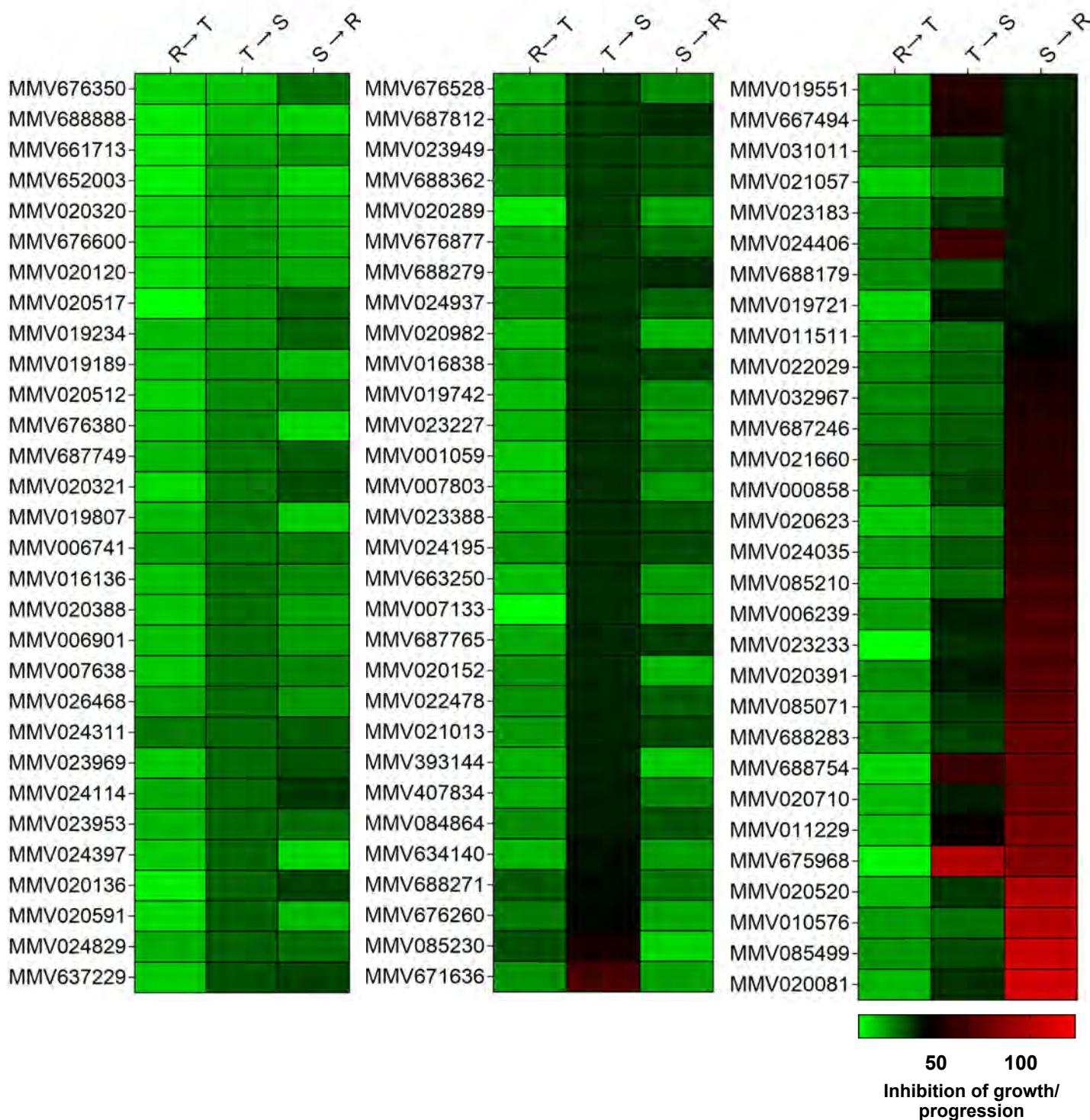


MMV020081

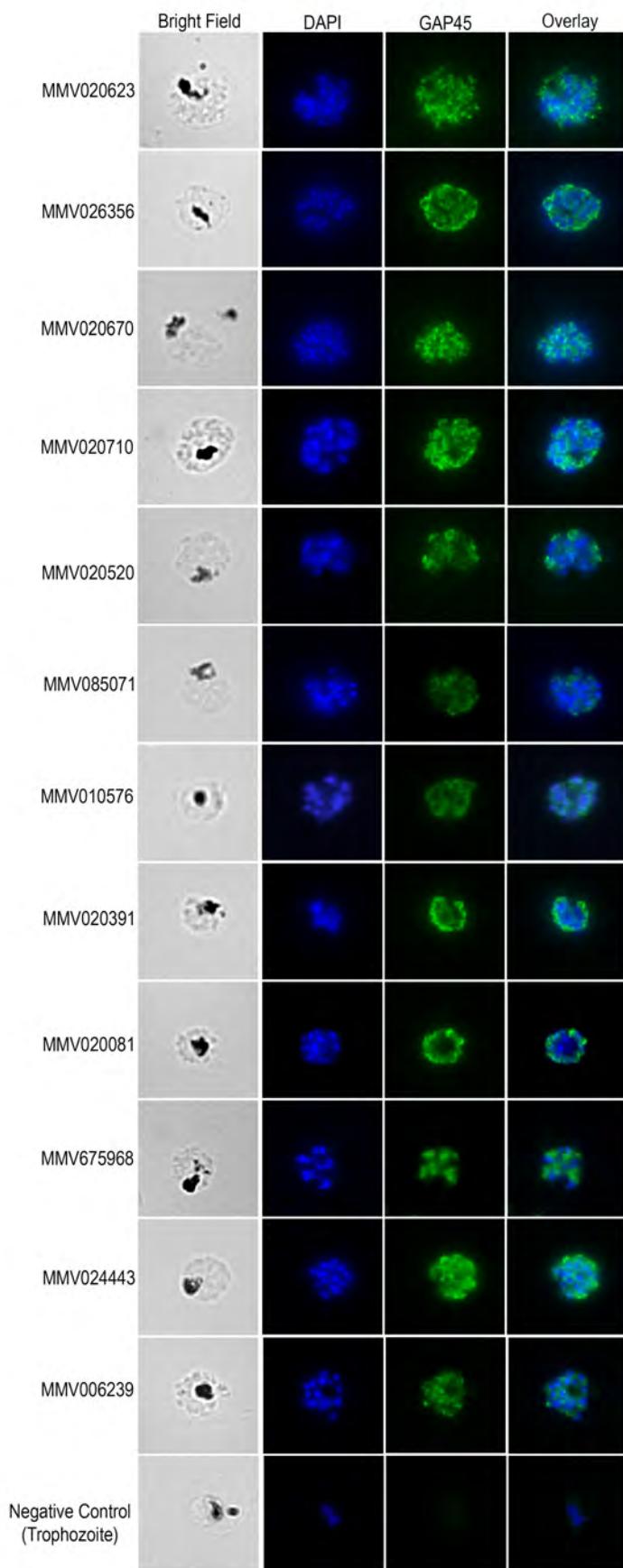


MMV675968

# Fig S2

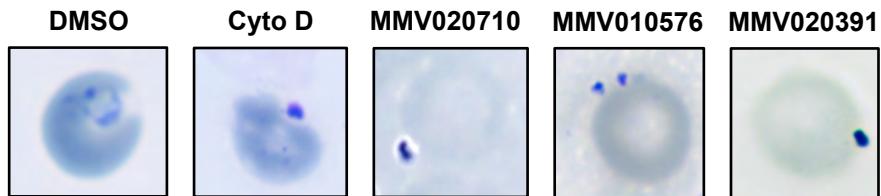


# Fig S3

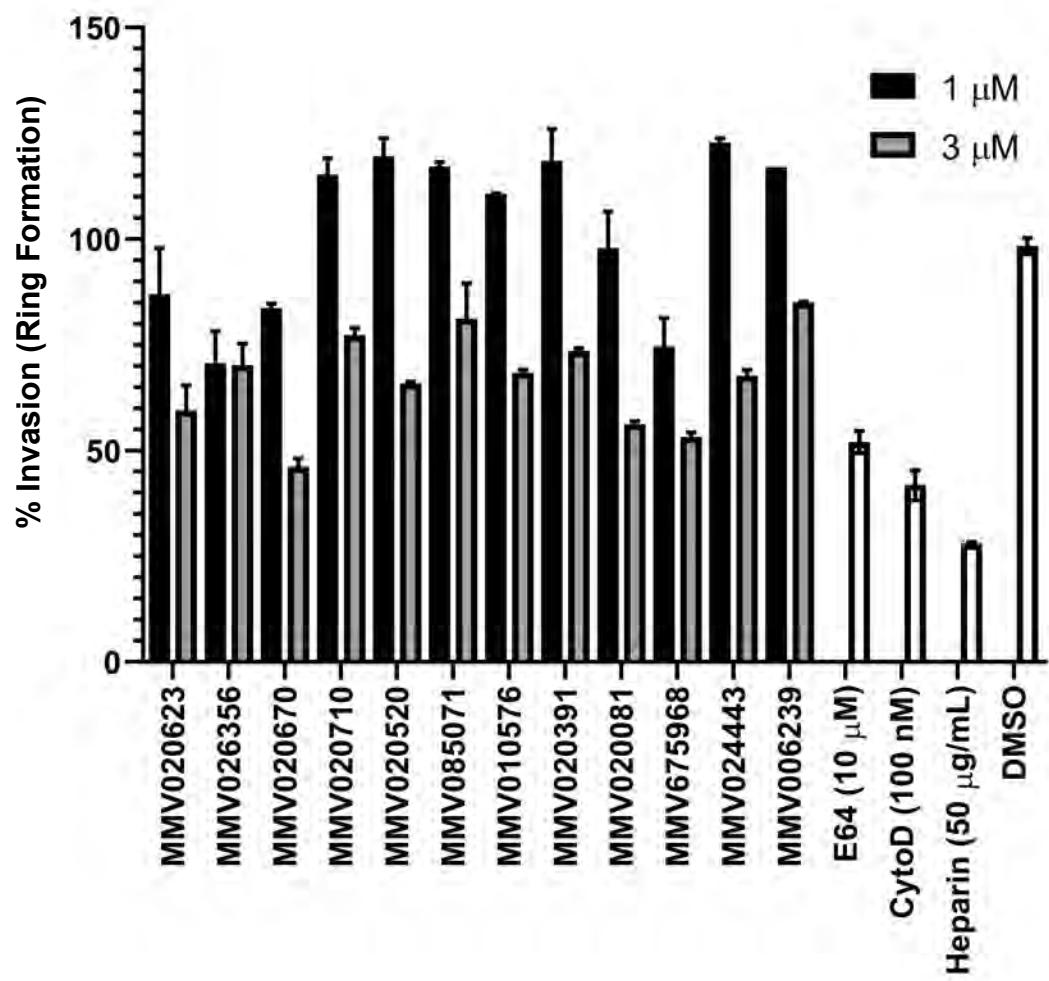


# Figure S4

A



B



**Supplementary Table 1: Molecules from other disease sets exhibiting antimalarial activity**

ChEMBL ID	Pathogen Box ID	Compound Class	Disease Set	Pfal IC50 ( $\mu$ M) (this study)	Cytotoxicity Data (Pathogen Box dataset)	Predicted Cellular Target
<b>CHEMBL227240</b>	MMV688514	Benzene carboximidamide	Kinetoplastids	3.66	2.64	—
<b>CHEMBL466426</b>	MMV688943	Difenoconazol	Kinetoplastids	6.18	0	—
<b>CHEMBL564829</b>	MMV676602	Milciclib	Kinetoplastids	6.06	<0.26	—
<b>CHEMBL2441383</b>	MMV652003	Benzamide	Kinetoplastids	0.11	0.413	Leucyl-tRNA synthetase <sup>1</sup>
<b>CHEMBL1981047/ CHEMBL384575/ CHEMBL402548</b>	MMV676600	Benzamide	Kinetoplastids	0.25	4.83	—
<b>CHEMBL1836562</b>	MMV688410	Acetamide	Kinetoplastids	3.85	16.4	—
<b>CHEMBL1197423</b>	MMV688547	1H-1,2,3-Triazole	Kinetoplastids	1.78	>80	DNA Targeted agent <sup>2-3</sup>
<b>CHEMBL3637895</b>	MMV688283	4-Quinolinamine	Kinetoplastids	0.50	8	Potentially target Beta-hematin formation <sup>4</sup>
<b>CHEMBL394241</b>	MMV676057	1-Piperazinecarboxylic acid	Kinetoplastids	6.51	4.03	—
<b>CHEMBL45843</b>	MMV688179	2,2'-[2,5-Furandiylbis(3-chlor-4,1-phenylene)] diguanidin	Kinetoplastids	0.74	6.75	—
<b>CHEMBL227667</b>	MMV688361	Isoxazole	Kinetoplastids	1.45	4.51	—
<b>CHEMBL3431105</b>	MMV595321	Benzamide	Kinetoplastids	5.59	0	—
<b>CHEMBL3637896</b>	MMV688371	Benzamide	Kinetoplastids	5.85	0	—
<b>CHEMBL474899</b>	MMV659004	Pyrimidine	Kinetoplastids	2.39	10.2	Methionine aminopeptidase <sup>5</sup>
<b>CHEMBL3637894</b>	MMV688274	4-Morpholineacetamide	Kinetoplastids	3.48	10.9	—
<b>CHEMBL1197424</b>	MMV688407	1H-1,2,3-Triazole	Kinetoplastids	2.92	22.9	—

<b>CHEMBL520654</b>	MMV688362	1H-Imidazole	Kinetoplastids	0.42	14.3	Binds to the DNA minor groove at AT-rich regions of DNA <sup>2</sup>
<b>CHEMBL1230468</b>	MMV688180	Benzenesulfonamide	Kinetoplastids	5.31	0.0454	—
<b>CHEMBL1836611</b>	MMV688279	4-Quinazolinol	Kinetoplastids	0.22	10	—
<b>CHEMBL238442</b>	MMV687706	Piperazine	Kinetoplastids	7.65	6.43	—
<b>CHEMBL413331</b>	MMV688271	Guanidine	Kinetoplastids	0.40	13.5	Binds to the DNA minor groove at AT-rich regions of DNA <sup>3</sup>
<b>CHEMBL3104375</b>	MMV689243	3-Pyridinamine	Kinetoplastids	2.00	25.8	Cytochrome P450 inhibitors <sup>6</sup>
<b>CHEMBL1897483/ CHEMBL3183941/ CHEMBL3637899</b>	MMV688754	Benzeneacetic acid	Kinetoplastids	0.01	0	—
<b>CHEMBL3637893</b>	MMV688273	4,6-Quinazolinediamine	Kinetoplastids	1.61	9.72	—
<b>CHEMBL472881</b>	MMV658988	4-Pyrimidinamine	Kinetoplastids	2.84	11.3	Methionine aminopeptidase <sup>5</sup>
<b>CHEMBL3637898</b>	MMV688550	Imidazo [1,2] purine	Kinetoplastids	3.05	44.3	—
<b>CHEMBL2097846</b>	MMV688889	pyrimidin-7-amine	Tuberculosis	8.24	NA	—
<b>CHEMBL2098256</b>	MMV688888	Pyrimidine	Tuberculosis	0.95	NA	—
<b>CHEMBL204432</b>	MMV661713	4-Pyrimidinamine	Tuberculosis	0.60	NA	Glutaminyl cyclase <sup>7-8</sup>
<b>CHEMBL2109905</b>	MMV688936	2-Furancarboxamide	Tuberculosis	6.60	NA	—
<b>CHEMBL1622353</b>	MMV676401	4-Quinazolinamine	Tuberculosis	5.99	18.59	—
<b>CHEMBL2098478</b>	MMV676449	1H-Benzimidazole-1-ethanol	Tuberculosis	8.51	43.2	—
<b>CHEMBL2098184</b>	MMV676477	Benzamide	Tuberculosis	0.76	1.34	—
<b>CHEMBL2098293</b>	MMV676512	1H-Imidazole-5-carboxamide	Tuberculosis	3.66	3.78	—
<b>CHEMBL2109740</b>	MMV687703	1H-Benzimidazole	Tuberculosis	4.03	24.98	—

<b>CHEMBL535116</b>	MMV023969	Isoquinoline	Tuberculosis	0.19	8.02	—
<b>CHEMBL531893</b>	MMV021660	Guanidine	Tuberculosis	0.07	6.46	Folate Pathway <sup>7, 9-10</sup>
<b>CHEMBL2098162</b>	MMV688122	2-pyrimidin-4-amine	Tuberculosis	5.53	14.26	Methionine aminopeptidase <sup>7, 11</sup>
<b>CHEMBL2109766</b>	MMV687749	Pyrimidine	Tuberculosis	0.85	29.03	Tyrosine Kinase <sup>7</sup>
<b>CHEMBL2109769</b>	MMV687248	1H-Benzimidazol-2-amine	Tuberculosis	1.41	31.5	—
<b>CHEMBL2109877</b>	MMV688125	Benzenesulfonamide	Tuberculosis	4.04	17.69	—
<b>CHEMBL561057</b>	MMV687273	SQ-109, In clinical trials 2012 TB	Tuberculosis	3.29	7.1	HMG-CoA reductase pathway <sup>10, 12-15</sup>
<b>CHEMBL580032</b>	MMV024311	1H-Indole	Tuberculosis	0.45	12.71	—
<b>CHEMBL2313136</b>	MMV687807	Benzamide	Tuberculosis	2.47	0.65	—
<b>CHEMBL3637864</b>	MMV687812	2-Pyrazinecarboxamide	Tuberculosis	0.26	3.86	—
<b>CHEMBL1397830</b>	MMV676411	Propanamide	Tuberculosis	5.02	29.29	—
<b>CHEMBL530275</b>	MMV021013	4-pyrimidinamine	Tuberculosis	0.72	NA	Methionine aminopeptidase <sup>7</sup>
<b>CHEMBL2109928</b>	MMV687765	Pyrimidine	Tuberculosis	0.47	14.08	Tyrosine Kinase <sup>7</sup>
<b>CHEMBL3637867</b>	MMV495543	Benzamide	Tuberculosis	0.26	47.64	—
<b>CHEMBL1242290</b>	MMV675993		Cryptosporidiosis	3.93	1.63	—
<b>CHEMBL88430</b>	MMV675968		Cryptosporidiosis	0.07	3.44	Dihydrofolate reductase <sup>16-18</sup>
<b>CHEMBL1626/315 157/1620822</b>	MMV637229	2-pyrimidin-4-amine	Hookworm Trichuriasis	0.01	9.28	—
<b>CHEMBL3637906</b>	MMV668727	Terpyridin-2'-amine	L. Filariasis- Onchocerciasis	3.64	>80	—
<b>CHEMBL3637912</b>	MMV676063	oxy-phenyl urea	L. Filariasis- Onchocerciasis	3.16	5.77	—
<b>CHEMBL3637903</b>	MMV671636	quinolinone	L. Filariasis- Onchocerciasis	0.01	>80	Mitochondria cytochrome bc <sub>1</sub> complex <sup>19</sup>

<b>CHEMBL3637922</b>	MMV688761	Benzamide	Schistosomiasis	3.46	6.94	—
<b>CHEMBL3637921</b>	MMV688763	pyridazinone	Schistosomiasis	2.17	1.55	—
<b>CHEMBL3637924</b>	MMV688766	5-methoxyphenol	Schistosomiasis	1.71	>80	—
<b>CHEMBL3637923</b>	MMV688552	1H-Pyrazole-1-carboxamide	Schistosomiasis	4.49	30.7	—
<b>CHEMBL3637929</b>	MMV688509	1-Piperidinecarboxylic acid	Toxoplasmosis	5.55	>50	—
<b>CHEMBL190228</b>	MMV688703	Pyridine	Toxoplasmosis	1.39	>50	cGMP-dependent protein kinase <sup>20</sup>

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